UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
[illegible]	

DATE MAILED: [illegible]

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/785,793	SERAPHIN ET AL.
Examiner	**Art Unit**
Ja-Na Hines	1645

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[X] Responsive to communication(s) filed on *13 November 2002*.

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[X] Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *12-28* is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[X] Claim(s) *1-11* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[X] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)[ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and or 121.

Attachment(s)

1)[ ] Notice of References Cited (PTO-892)
2)[ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)[ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4)[ ] Interview Summary (PTO-413) Paper No(s).
5)[ ] Notice of Informal Patent Application (PTO-152)
6)[ ] Other:

Notice of References Cited

Application Control No	Applicant(s) Patent Under Reexamination
09/785,793	SERAPHIN ET AL
Examiner	**Art Unit**
Ja-Na A Hines	1645

U.S. PATENT DOCUMENTS

*		Document Number (Country, Code-Number-Kind Code)	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number (Country, Code-Number-Kind Code)	Date MM-YYYY	Country	Name	Classification
*	N	EP 1,231,276 A1	08-2002	Europe	Seraphin et al.	C12N 15/74
*	O	WO 96/40943	12-1996	Europe	Darzins et al.	C12N 15/62
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		(Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Panagiotidis et al. 1995. Gene. 164: 45-47.
*	V	Zheng et al. 1997. Gene. 186: 55-60.
	W	
	X	

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 11 is acknowledged. Claims 1-11 are under consideration in this office action.

Priority

2 Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Europe on 17 August 1999. It is noted, however, that applicant has not filed a certified copy of the European application as required by 35 U.S.C. 119(b).

Drawings

3 The corrected or substitute drawings were received on February 16, 2001. These drawings are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 drawn to a method for detecting and/or purifying substances selected from subunits thereof. The written description in this case sets forth specific polypeptides and proteins selected for detection or purification, therefore the written description is not commensurate in scope with the claims drawn to subunits thereof. Neither the specification nor the claims teach how to define subunits thereof. Neither the claims nor the specification teach how to obtain such subunits. There is no guidance as to what the subunits are; or what subunits can or cannot be used in the method claimed. The specification does not include structural examples of analogs or fragments. Thus, the resulting subunit could result in a method not taught and/or enabled by the specification.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of specifically named proteins and polypeptides, the skilled artisan cannot envision the detailed structure of the subunits thereof, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of

isolating it. Furthermore, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

Therefore only the recited proteins and polypeptides and not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

5 Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like TEV and NIA must be spelled out when used for the first time in a chain of claims

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6 Claims 1-9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Darzins et al., (WO 96/40943). Darzins et al., teach the construction and use of expression vectors comprising a method for expressing proteins whereby the desired

protein product is secreted and purified (page 8-9 lines 28-2). The methods teach the construction and use of host/vector systems that use proteins or heterologous protein configurations fused to a combination of polyhistidine tags and protein A IgG binding domains of Staphylococcus, Factor Xa or Tobacco Etch Virus (TEV) protease cleavage sites (page 9 lines 10-14). The recombinant proteins can then be purified after cleavage with a specific protease or from culture medium (page 9 lines 16-19). The construction of heterologous fusion proteins, includes small DNA fragments containing the recognition sequences that can be placed between the DNA sequences that encode the amino and carboxy terminal sorting signal whereby this multiple cloning site will facilitate the insertion of heterologous protein coding sequences and upon expression will generate in-frame protein fusions (page 13 lines 5-11). This is equivalent to an expression environment containing one or more heterologous nucleic acids encoding one or more polypeptides of a biomolecule complex. The expression vector systems are suitable for overproducing and purifying any desired protein (page 14 lines 6-8). Cleavage sites for various proteolytic enzymes can be engineered into the expression vectors so that the cleavage sites reside in multiple locations of the peptide (page 14 lines 13-16). Proteases that may be suitable include tobacco etch virus, TEV (page 14 lines 17-20). The most preferred protease is the TEV NIa proteinase which cleaves a specific consensus cleavage site (page 14 lines 29-16). This is the same specific proteolytic cleavage site for TEV protease NIA as claimed. Following protease treatment the released protein can be purified in a variety of ways known in the art including affinity chromatography (page 15 lines 17-21). Affinity chromatography is well

known in the art of purification by means of using affinity for another substance immobilized on a solid support; for instance an antigen is purified by affinity chromatography on a column of specific antibody molecules covalently linked to beads.

A single step purification using affinity tags can be engineered at either the amino or carboxy terminal regions of the fusion proteins (page 15 lines 23-24). Useful affinity tags include polyhistidine tags, IgG binding domain of protein A and glutathione S-transferase (page 15 lines 24-27). Recombinant proteins can be easily purified using metal chelation such as Ni-agarose chromatography methods (page 5 lines 27-30). Moreover, affinity tags can be easily removed by incorporating protease cleavage sites (page s 15-16 lines 30-2). Example 1 teaches construction of anchored vectors and DNA fragments encoding heterologous protein sequences. Example 2 teaches expression of recombinant genes whereby recombinant proteins can be detected using polyclonal antisera against the molecule, or monoclonal antibodies directed against specific antigens (page 21 lines 5-9). Example 3 teaches purification of recombinant proteins whereby the fusion proteins containing polyhistidine residues can be purified by passing the supernatant over a nickel-chelating resin and further eluting the proteins (pages 21-22 lines 26-4).

Therefore, Darzins et al., teach a method for detecting and/or purifying substances providing an expression environment containing heterologous nucleic acids with cleavage sites encoding at the two subunits of biomolecules, fused to at least two different affinity tags; maintaining the expression environment to allow expression of the fusion proteins with the affinity tags and detecting and or purifying the polypeptide

whereby the binding of the polypeptide occurs via one affinity tag being bound to a support material.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Darzins et al., (WO 96/40943) in view of Zheng et al. Darzins et al., (WO 96/40943) has been discussed above, however Darzins et al., does not teach affinity tags consisting of at least one calmodulin binding peptide.

Zheng et al., teach expression vectors for high level protein production, one-step purification and direct labeling of calmodulin-binding peptide (CBP) fusion proteins. CBP proteins can be used in calmodulin affinity chromatography methods (abstract). A common strategy employed to facilitate the purification of recombinant proteins is to fuse the proteins of interest to another peptide or protein, i.e., affinity tags, which have specific ligand and hence can rapidly and efficiently purify the protein (page 55 para. 2). Other popular affinity tags include polyhistidine tags, protein A, and epitopes for different antibodies (pages 55-56 para. 2). The CBP tag is small and less likely to affect

the biological function of the recombinant fusion protein of interest (page 56 para 1). The CBP tag can be effectively removed by cleavage with thrombin (page 56 para. 2). Thus CBP can be expressed with recombinant fusion proteins, used in affinity chromatography assays and removed from fusion proteins.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to exchange the affinity tags used the method for detecting and/or purifying substances providing an expression environment as taught by Darzins et al., in view of the affinity tag of Zheng et al., because Zheng et al., teach that calmodulin binding proteins can be expressed with recombinant fusion proteins, used in affinity chromatography assays and removed from fusion proteins. One would have a reasonable expectation of success because one having ordinary skill in the art would have been motivated to make such a change as a mere alternative or equivalent affinity tag since Zheng et al, teach affinity chromatography and other popular tags are known in the art of affinity purification and the expected detection and purification results would have been obtained since the prior art clearly teaches the detection and purification of similar and equivalent affinity tags. Moreover, the use of alternative and functionally equivalent affinity tags would have been desirable to those of ordinary skill in the art based on their ability to be expressed within recombinant fusion proteins, their use in affinity chromatography assays and there ability to be removed from fusion proteins.

Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. EP 1,231,276 teach methods for purifying biomolecules of protein complexes. Panagiotidis et al., teaches a dual tag prokaryotic expression vector for the purification of full-length proteins.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
January 21, 2003